Pharmacokinetics of moxifloxacin, a novel 8-methoxy-quinolone, in patients with renal dysfunction

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Aims To evaluate the influence of impaired renal function on the plasma and urinary pharmacokinetics of moxifloxacin, a novel 8-methoxy-quinolone antibacterial drug.
Methods Twenty male and 12 female subjects (8 healthy subjects, 24 patients with impaired renal function), 18–75 years of age were investigated in parallel fashion with four groups stratified according to creatinine clearance (CL_{CR}; $n=8$ for each group). The pharmacokinetics of moxifloxacin and the metabolites M1 (sulphonate metabolite) and M2 (glucuronide) in plasma and urine were determined repeatedly up to 96 h after single oral doses of 400 mg. Patients were monitored intensively with regard to clinical and laboratory safety and tolerability.
Results Single doses of 400 mg moxifloxacin were safe and well tolerated. The urinary excretion of moxifloxacin (Ae_{ur}, P: 0.0002) and renal clearance (CL_R, $P<0.0001$) were reduced with decreasing CL_{CR}, mean C_{max} was slightly reduced (C_{max}-ratio 85.0%, 90% CI 67.9, 106.4% severe renal impairment *vs* healthy subjects) but the AUC was unchanged even in severe renal impairment (AUC-ratio 101.3%, 90% CI 79.7, 128.6%). The mean AUC of the N-sulphonate M1 was slightly increased (by about 53% for the most severe disease) by impaired renal function, but there was no significant correlation between individual AUC and CL_{CR}, whilst Ae_{ur} and CL_R were significantly correlated with CL_{CR}. In contrast, for the acylglucuronide M2, Ae_{ur} (P: 0.0026), CL_R ($P<0.0001$) and AUC (P: 0.0011) were directly correlated with CL_{CR}.
Conclusions Renal dysfunction had little effect on the plasma pharmacokinetics of either moxifloxacin or metabolite M1, although their renal clearance and urinary excretion were reduced. In contrast renal dysfunction did result in changes in the plasma pharmacokinetics of metabolite M2, causing greater and longer exposure. However the extent of these changes is unlikely to be of clinical relevance.

Keywords: moxifloxacin, pharmacokinetics, renal impairment

Introduction

Moxifloxacin (8-methoxy-1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0.]-non-8-yl-6-fluoro-1,4-dihdro-4-oxo-3-quinoline carboxylic acid, $C_{21}H_{24}FN_3O_4$.HCl) is a new oral 8-methoxy-quinolone, developed by Bayer AG [1]. It has antibacterial properties that differ from those of other quinolones. While still active against Gram-negative pathogens, it is also highly effective against Gram-positive cocci (including enterococci), aerobic, intracellular bacteria, and 'atypical' organisms such as *Mycoplasma* and *Chlamydia*. It is also active against anaerobic bacteria. On the other hand, *Pseudomonas aeruginosa* is generally not affected by moxifloxacin. Moxifloxacin is effective against pathogens of the respiratory tract, skin and skin structures and other sites likely to be involved in community acquired infections. *Streptococcus pneumoniae*, which shows increasing resistance to β-lactam antibiotics is also included in its spectrum of activity. Indeed the potency of moxifloxacin against Gram-positive pathogens is 20–50 times higher than that of ciprofloxacin or ofloxacin [2, 3].

The pharmacokinetics of moxifloxacin were found to be linear and proportional to dose within a range of single i.v. doses of 100–400 mg [4], single oral doses of 50–800 mg [5] and repeated oral doses of 100–200 mg

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twice daily and 400–600 mg once daily [6]. Upon repeated dosing, no excessive accumulation was observed [6]. Moxifloxacin is readily absorbed from the gastrointestinal tract and not subject to presystemic biotransformation. Thus its oral bioavailability is high (approximately 90% [7]) and maximum concentrations (C_{max}) are reached within 1–4 h (t_{max}) after dosing. The oral bioavailability of moxifloxacin is not altered by pretreatment with ranitidine [8] and dairy products [9] and absorption is only slightly delayed by administration at the end of a standard fat-rich meal [10]. Bioavailability is reduced by concomitant administration of complex chelators such as antacids [8] and iron supplements [11]. Moxifloxacin is about 45% protein bound and penetrates readily in target tissues and fluids [12]. Its distribution volume is about 2.5 l kg^{-1} [7].

Moxifloxacin is cleared both renally and nonrenally with a total plasma clearance of about 12 l h^{-1} and a renal clearance of about 3 l h^{-1} [7]. Up to 20% of the drug is excreted unchanged in urine and approximately 25–26% is recovered from faeces [7]. Moxifloxacin is mainly metabolized to an N-sulphonate (metabolite M1) and an acylglucuronide (metabolite M2). These phase II conjugates are pharmacologically inactive and there is no evidence of their *in vivo* deconjugation. Approximately 14% of the dose is excreted via the kidneys in the form of M2 ($f_u \sim 95\%$) by active tubular secretion. Metabolite M1 ($f_u \sim 10\%$) is mainly excreted into the faeces where it accounts for about 37–38% of the dose [7], while only 3% of the dose is recovered in urine (active tubular secretion). There is no relevant interaction with theophylline, warfarin [13], or probenecid [14].

Moxifloxacin is likely to be used in some patients with impaired renal function. The present study evaluated whether renal impairment alters the plasma and urinary pharmacokinetics of moxifloxacin and its M1 and M2 metabolites.

Parts of the results have been published [15].

Methods

Subjects

Twenty males and 12 females (8 healthy subjects, 24 patients with impaired renal function), 18–75 years of age (mean: 54, s.d.: 11, range: 23–74 years) were investigated and completed the study in accordance with the protocol. Four groups, each of eight subjects, were studied in parallel, stratified according to their creatinine clearance (CL_{CR}) measured about 1 week before the investigations:

Group 1: $CL_{CR} > 90$ ml min^{-1} 1.73 m^2 (young healthy subjects)
Group 2: $60 < CL_{CR} \leq 90$ ml min^{-1} 1.73 m^2
Group 3: $30 < CL_{CR} \leq 60$ ml min^{-1} 1.73 m^2
Group 4: $CL_{CR} \leq 30$ ml min^{-1} 1.73 m^2 (not on dialysis).

All subjects provided written informed consent. The study protocol was subject to approval by an independent ethics committee (the local medical council, Kiel, Germany). The study was conducted in accordance with the Declaration of Helsinki (amended Somerset West, 1996), the Notes of Guidance on GCP [16] and the German Drug Law (AMG).

Design

The study was conducted as a single centre, single dose, non-randomized, non-blinded, non-controlled, parallel group comparison. Subjects were assigned to one of four protocol-defined groups according to their CL_{Cr} as determined within 1 week prior to dosing. Each subject received a single oral dose of 400 mg moxifloxacin administered with 100 ml CO_2-free water after an overnight fast.

Assessments

Venous blood samples for the determination of moxifloxacin and its metabolites in plasma were sampled at the following times: before dosing (0 h) and then at 15 min, 30 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 : 00, 32, 48, 72 and 96 h after dosing. On each occasion 3 ml of venous blood was collected in NH_4-heparinate coated tubes; the samples were centrifuged for 5 min at 1600 *g* and 5° C within 15 min after collection. Plasma was then transferred to polypropylene tubes, frozen and stored at −20° C until subsequent analytical determination.

Urine was collected over the following periods: a predose assay blank and then 0–4, 4–8, 8–12, 12–24, 24–48, 48–72 and 72–96 h after dosing. The volume of each fraction was recorded and a 5 ml aliquot was frozen and stored at −20° C until analysis.

Drug and metabolite analysis

Concentrations of moxifloxacin and metabolites M1 and M2 in plasma and urine were determined by a validated and h.p.l.c. method with fluorescence detection [17]. First the long-term stability of the analytes was investigated at −20° C in plasma and urine and short-term stability in plasma, urine, aqueous solutions at various temperatures (4° C, room temperature, 37° C) over the time between sampling to freezing for whole blood and plasma, and that from thawing to analysis. At room temperature compounds were stable for at least 2 days in plasma, urine and aqueous solution, under long-term storage

conditions stability results over more than 1 year indicate the suitability of the analytical method to quantify the parent drug and metabolites. The limits of quantification were 10, 25 and 40 $\mu g\,l^{-1}$ for moxifloxacin, metabolite M1 and M2, respectively. Quality control samples produced from blank plasma spiked with known concentrations of the analytes at three levels (high, medium, low) were stored and analysed together with the study samples. Interday precision (specification: $\leq 20\%$ throughout the working range) ranged from 2.8 to 3.6% (plasma) and from 1.9 to 5.0% (urine) within the working range of the method (19.4% at the limit of quantification for plasma). Accuracy (specification: 90–110% throughout the working range) were always within these limits ranging from 99.6–105.2% (plasma) and 101.3–103.8 (urine).

Pharmacokinetic analysis

The plasma and urinary pharmacokinetics of moxifloxacin and its metabolites were analysed by conventional non-compartmental approaches [18]. Peak concentrations (C_{max}) and time to reach C_{max} (t_{max}) were directly determined from the individual plasma concentration *vs* time profiles. AUC (area under the curve after single dose administration extrapolated to infinity) determination was based on the linear trapezoidal method in the ascending part of the plasma concentration *vs* time curve and the log-linear trapezoidal rule in the declining part. AUC_{norm} and $C_{max,norm}$ were calculated by normalizing the AUC and C_{max} data to the dose and the body weight. λ_z (apparent terminal log-linear disposition rate constant) was derived from the terminal slope of the logarithmic plasma concentration *vs* time profile. $t_{1/2}$ (apparent terminal half-life) was obtained by linear regression analysis after log-transformation of the data using not less than three data points. The mean residence time (MRT) was determined as AUMC/AUC, where AUMC is the area under the first moment of the concentration time curve determined by integrating the product of time and concentration from 0 to infinity. The apparent oral volume of distribution during terminal phase (V_z/F) was calculated as $[CL/F]/\lambda_z$ with CL/F as the apparent oral clearance (CL/F calculated as Dose/AUC). In order to evaluate the renal excretion the amount excreted unchanged into urine (Ae_{ur}) and the renal clearance (CL_R calculated from the urinary excretion and the plasma $AUC_{0,tn}$ from the expression $Ae_{ur}/AUC_{0,tn}$) were determined.

Statistical analyses

C_{max} and AUC were assumed to arise from log-normal distributions. The log-transformed C_{max}, $C_{max,norm}$, AUC and AUC_{norm} were analysed for group effects by ANOVA. The point estimates of the true patient and healthy subject ratios were re-transformed from the difference of the ANOVA adjusted least square means of the log-transformed individual values. The mean square error of the ANOVA was used as variance estimate to calculate the corresponding 90% confidence interval (CI) of the true group ratios. Spearman's rank test was used to define the relationship between CL_{CR} and individual pharmacokinetic parameters.

Results

Clinical observations

All 32 subjects completed the study in accordance with the protocol. Single oral doses of 400 mg moxifloxacin were in general well tolerated. None of the healthy subjects and none of the subjects in group 3 experienced adverse events (AEs). In group 2, 4/8 subjects experienced 6 AEs (mild headache, mild diarrhoea, mild and moderate asthenia, moderate arthralgia and mild nausea). In group 4 (severely impaired renal function), 7 AEs were recorded for 2/8 subjects. In this latter group 6/7 of the reported events were mild and moderate elevations of serum lipase and amylase values already present before dosing. Supine blood pressure and heart rate (measured repeatedly) were not affected by treatment. Significant findings, if any, were already present pre-dose (mainly hypertension related to the underlying disease) and did not worsen under treatment.

Pharmacokinetics of moxifloxacin

The time courses of the geometric mean plasma concentrations for each treatment group are shown in Figure 1. The respective pharmacokinetic measurements are summarized in Table 1. There was no group effect

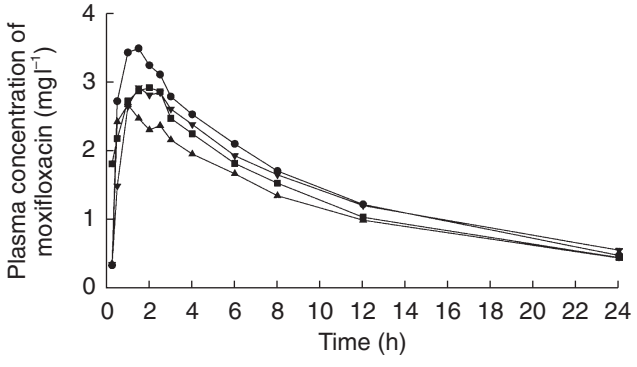

Figure 1 Geometric mean plasma drug concentration *vs* time courses after single oral doses of 400 mg moxifloxacin in healthy subjects (group 1, $CL_{CR} > 90$ ml min^{-1} 1.73 m^2, ●) and in patients with renal impairment (group 2, $CL_{CR} \leq 90$ ml min^{-1} 1.73 m^2, ■; group 3 $CL_{CR} \leq 60$ ml min^{-1} 1.73 m^2, ▲; group 4, $CL_{CR} \leq 30$ ml min^{-1} 1.73 m^2, ▼, $n = 8$ per group).

Table 1 Pharmacokinetic parameters of moxifloxacin after administration of single 400 mg oral doses to healthy subjects and to patients with different degrees of renal impairment stratified in four groups of eight subjects each. (geometric mean/geometric s.d. (range)).

Parameter	*Group 1*	*Group 2*	*Group 3*	*Group 4*
CL_{CR} *(ml min^{-1} 1.73 m^2)*	*> 90*	*> 60 and ≤ 90*	*> 30 and ≤ 60*	*≤ 30*
n	*8*	*8*	*8*	*8*
AUC (mg l^{-1} h)	43.40/1.4	40.08/1.3	35.77/1.4	43.95/1.3
	(28.60–75.70)	(29.60–55.00)	(22.90–58.00)	(25.10–60.10)
AUC_{norm} (kg l^{-1} h)	7.09/1.3	7.34/1.3	7.44/1.3	8.46/1.4
	(4.65–9.84)	(5.19–11.70)	(5.15–10.70)	(4.07–12.00)
C_{max} (mg l^{-1})	4.38/1.4	4.92/1.4	3.45/1.5	3.16/1.2
	(2.61–6.60)	(3.04–6.74)	(1.89–6.04)	(2.63–4.07)
$C_{max,norm}$ (kg l^{-1})	0.72/1.3	0.90/1.3	0.72/1.4	0.61/1.2
	(0.52–0.95)	(0.54–1.28)	(0.43–1.15)	(0.43–0.69)
$t_{1/2}$ (h)	14.9/1.5	15.2/1.2	16.2/1.2	14.5/1.2
	(8.6–30.3)	(12.4–19.2)	(12.2–20.0)	(10.4–17.7)
MRT (h)	15.1/1.3	15.1/1.2	16.7/1.1	17.2/1.3
	(9.2–22.5)	(12.7–23.2)	(14.2–19.7)	(10.0–22.1)
V_z/F (l kg^{-1})	3.0/1.4	3.0/1.3	3.1/1.2	2.5/1.3
	(2.3–6.3)	(2.2–4.1)	(2.5–4.3)	(1.9–3.7)
CL/F (l h^{-1})	9.2/1.4	10.0/1.3	11.2/1.4	9.1/1.3
	(5.3–14.0)	(7.3–13.5)	(6.9–17.5)	(6.7–16.0)
CL_R (l h^{-1})	2.3/1.3	2.0/1.3	1.9/1.5	0.9/1.4
	(1.8–3.2)	(1.5–2.8)	(1.1–2.9)	(0.6–1.7)
Ae_{ur} (24 h) (%)	24.2/1.4	19.5/1.3	16.4/1.7	9.5/1.6
	(12.8–35.4)	(15.3–37.1)	(6.6–26.1)	(3.6–16.8)
t_{max} [1)] (h)	0.77	0.25	0.75	1.50
	(0.50–1.50)	(0.25–2.50)	(0.50–2.50)	(0.50–2.52)

1): median and range.

for AUC ($P=0.45$) and AUC_{norm} ($P=0.59$), whilst there was a significant group effect for C_{max} ($P=0.03$) and $C_{max,norm}$ ($P=0.05$). This group effect mainly related to somewhat lower C_{max} values in the patients with severely impaired renal function. The estimated patient : healthy subject ratios ($CL_{CR} > 90$ ml min^{-1} 1.73 m^2) were 126% (90% CI: 101, 158%), 100% (90% CI: 80, 125%) and 85% (90% CI: 68, 106%) for groups 2 ($60 < CL_{CR} \leq 90$), 3 ($30 < CL_{CR} \leq 60$) and 4 ($CL_{CR} \leq 30$), respectively. There was a significant correlation between the individual C_{max} ($r_s=0.438$, $P=0.012$), CL_R ($r_s=0.6405$, $P=0.0001$) and Ae_{ur} ($r_s=0.613$, $P=0.0002$) and CL_{CR}. Exposure to moxifloxacin in terms of AUC was independent of the degree of renal impairment (estimated ratio for group 4 : group 1: 101, 90% CI 80, 129%). The total amount of moxifloxacin excreted in urine was larger in the subjects with normal renal function, but there was no difference with regard to the pattern of excretion with time (Figure 2).

Pharmacokinetics of metabolites M1 and M2

The plasma concentrations of the N-sulphonate (M1) were not much affected by changes of renal function (Figure 3). The relatively low urinary excretion Ae_{ur} (mean values were 4.0, 2.7, 2.5 and 1.0% for groups 1 to 4, respectively) and the renal clearance CL_R (mean values were 11.3, 9.9, 8.6 and 1.8 l h^{-1} for groups 1 to 4, respectively) were significantly correlated with CL_{CR} (Ae_{ur}: $r_s=0.620$, $P=0.0002$; CL_R: $r_s=0.703$, $P<0.0001$).

In contrast, the AUC ($P=0.0167$) but not the C_{max} ($P=0.3042$) of the acylglucuronide (M2), which is predominantly cleared via urine, was significantly increased in renal dysfunction (Figure 4). AUC ($r_s=-0.565$, $P=0.0011$), CL_R ($r_s=0.736$, $P<0.0001$) and Ae_{ur} ($r_s=0.514$, $P=0.0026$) were significantly correlated with CL_{CR}.

Discussion

Moxifloxacin is readily absorbed and highly bioavailable after oral dosing. It penetrates extensively into target tissues and is cleared relatively slowly allowing for once daily dosing. Elimination is via the kidney (~20% of total drug clearance), biliary/faecal (~25% of clearance) excretion and phase II conjugation (~52%, M1: 38%; M2: 14% of clearance).

The present study demonstrates that the plasma pharmacokinetics of moxifloxacin are hardly affected by impairment of renal function. As anticipated, its

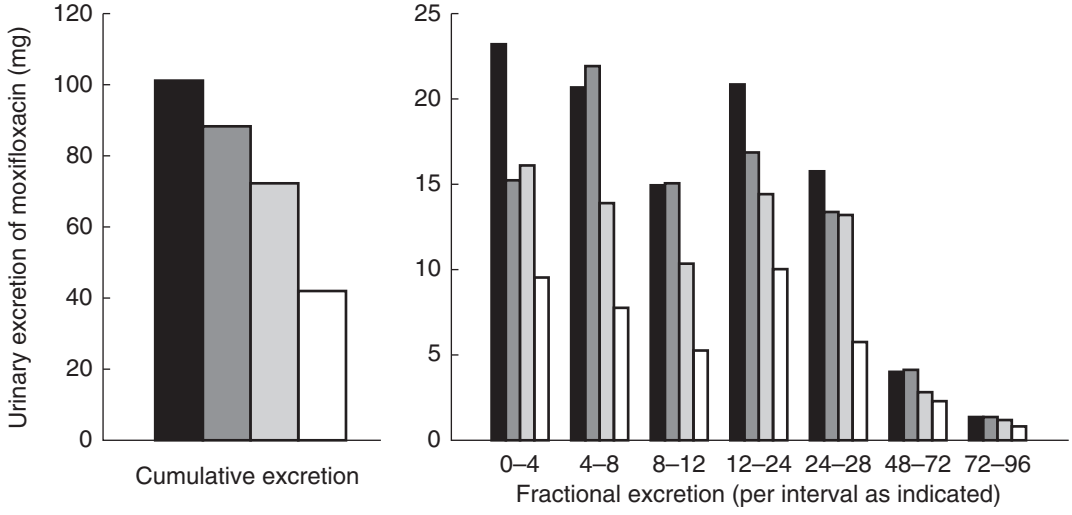

Figure 2 Geometric mean cumulative (Ae_{ur}, mg; left panel) and fractional (mg; right panel) urinary excretion of moxifloxacin after single oral doses of 400 mg moxifloxacin in healthy subjects (group 1, $CL_{CR} > 90$ ml min^{-1} 1.73 m^2, ■) and in patients with renal impairment (group 2, $CL_{CR} \leq 90$ ml min^{-1} 1.73 m^2, ■; group 3 $CL_{CR} \leq 60$ ml min^{-1} 1.73 m^2, ■; group 4, $CL_{CR} \leq 30$ ml min^{-1} 1.73 m^2, □, $n = 8$ per group).

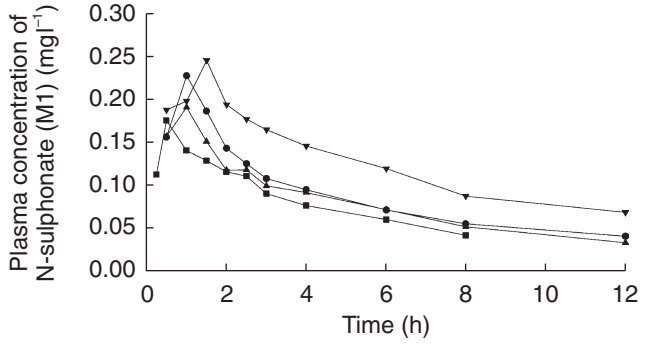

Figure 3 Geometric mean plasma concentration *vs* time courses of the N-sulphonate (M1) metabolite of moxifloxacin after single oral doses of 400 mg moxifloxacin in healthy subjects (group 1, $CL_{CR} > 90$ ml min^{-1} 1.73 m^2, ●) and in patients with renal impairment (group 2, $CL_{CR} \leq 90$ ml min^{-1} 1.73 m^2, ■; group 3 $CL_{CR} \leq 60$ ml min^{-1} 1.73 m^2, ▲; group 4, $CL_{CR} \leq 30$ ml min^{-1} 1.73 m^2, ▼, $n = 8$ per group).

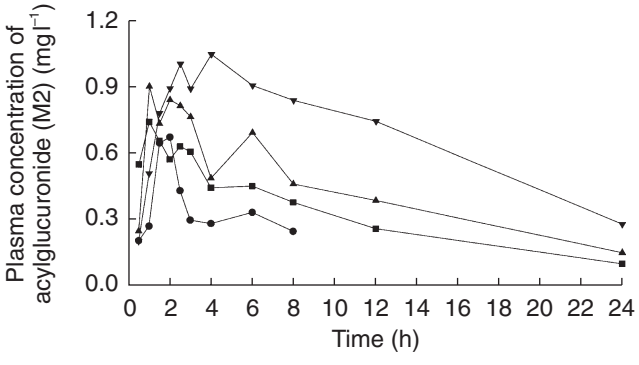

Figure 4 Geometric mean plasma concentration *vs* time courses of the acylglucuronide metabolite (M2) of moxifloxacin after single oral doses of 400 mg moxifloxacin in healthy subjects (group 1, $CL_{CR} > 90$ ml min^{-1} 1.73 m^2, ●) and in patients with renal impairment (group 2, $CL_{CR} \leq 90$ ml min^{-1} 1.73 m^2, ■; group 3 $CL_{CR} \leq 60$ ml min^{-1} 1.73 m^2, ▲; group 4, $CL_{CR} \leq 30$ ml min^{-1} 1.73 m^2, ▼, $n = 8$ per group).

urinary excretion and renal clearance were reduced with decreasing creatinine clearance. Theoretically an increase of up to approximately 40% in exposure to moxifloxacin could be expected when assuming complete loss of renal function and linear pharmacokinetic behaviour.

The overall exposure to the N-sulphonate M1 was slightly increased by impaired renal function. There was no significant correlation between the AUC of the metabolite and CL_{CR}, although the urinary excretion (Ae_{ur}) and renal clearance (CL_R) were significantly correlated with CL_{CR}. This finding is not unexpected because M1 is eliminated almost exclusively via the biliary/faecal route, contributing approximately 40% (< 5 l h^{-1}) to the total clearance of moxifloxacin in healthy subjects [7].

In contrast, for the acylglucuronide M2 Ae_{ur} and CL_R were directly correlated and the AUC, $t_{1/2}$ and MRT were inversely correlated with CL_{CR}. The observed accumulation of M2 in the plasma can be attributed to the blockade of its elimination pathway as only active tubular secretion into the urine is described for M2 in healthy human subjects [7].

These findings were further corroborated by pharmacokinetic results obtained in patients with mild to moderate liver cirrhosis, where the impairment of the biliary/faecal excretion pathway led to an increase in the

concentrations of metabolite M1, while the pharmacokinetics of the acyl glucuronide and the parent drug were not substantially changed [19].

The balanced renal, non-renal and elimination pattern of moxifloxacin reduces the influence of renal dysfunction on its overall pharmacokinetics [7]. Our findings indicate that no dosage adjustment is required in patients with renal impairment.

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